Original Article

The Pattern of Steroid Sensitivity and Steroid Resistance in Childhood Idiopathic Nephrotic Syndrome: A 5-Year Retrospective Observational Descriptive Study in a South-East Nigerian Tertiary Hospital

NR Mbanefo, FN Ogbuka[1], CA Nwaoha[2], CL Odimegwu, SN Uwaezuoke, HU Okafor

Department of Paediatrics, University of Nigeria Teaching Hospital, Ituku-Ozalla, [1]Department of Paediatrics, Enugu State University of Science and Technology Teaching Hospital, Parklane, Enugu, [2]Department of Paediatrics, Federal Medical Center, Owerri, Imo, Nigeria

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Abstract

Background/Aim: Nephrotic syndrome is the most common glomerular disease of childhood. Majority of the idiopathic cases frequently respond to steroid therapy and are regarded as steroid-sensitive nephrotic syndrome. Several studies have reported a change in this usual pattern to steroid-resistant nephrotic syndrome in Nigerian children. This study aimed to determine the pattern of steroid sensitivity and steroid resistance in childhood idiopathic nephrotic syndrome seen at a tertiary hospital in Enugu, south-east Nigeria. **Materials and Methods:** A retrospective study conducted in children with idiopathic nephrotic syndrome seen at the University of Nigeria Teaching Hospital, Ituku-Ozalla Enugu, over 5 years (from 2016 to 2020). The demographic variables, clinical data, and histopathological pattern were documented. Renal biopsies were studied by light microscope only. **Results:** Of a total of 150 patients, 105 (70%) were males, while 45 (30%) were females. Ninety six (64%) were aged 1-10 years. Fifty four (36%) were aged 11-18 years. Forty eight (32%) were aged 1-5 years. Mean age was 8.67 ± 4.69 years. One hundred and six (71%) initially had steroid-sensitive nephrotic syndrome; 12 (11.3%) and seven (6.6%) later became frequent-relapsers and steroid-dependent, respectively. Forty four (29.3%) had steroid-resistant nephrotic syndrome. Sixty eight had renal biopsy; the most common indication being steroid-resistance. The most common histological pattern was focal segmental glomerulosclerosis seen in 63.2% of these patients. Only four (9%) had renal transplant. **Conclusion:** Although the prevalence of steroid-sensitive nephrotic syndrome is higher in this clime, there is a rising incidence of steroid-resistant pattern attributed to incident cases of focal segmental glomerulosclerosis.

Keywords: *Childhood nephrotic syndrome, focal segmental glomerulosclerosis, Nigeria, steroid resistance, steroid sensitivity*

Introduction

Childhood nephrotic syndrome (CNS) refers to a clinical entity characterized by massive proteinuria, hypoalbuminemia, and generalized body swelling; it is the most common glomerular disease of childhood affecting approximately 2-16 per 100,000 children per year.[1] In the southeast Nigerian city of Enugu, it accounts for about 40.5% of all renal disorders.[2] Globally, majority of CNS are idiopathic; they frequently respond to steroid therapy and are thus regarded as steroid-sensitive nephrotic syndrome (SSNS).[1] However, this steroid-sensitivity varies across geographical regions depending on disease type, its possible etiology, and the underlying genetics.[1,3-6]

In multiracial countries, especially among the black population, several studies have documented a change

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Address for correspondence: Dr. NR Mbanefo, Department of Paediatrics, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria.
E-mail: ngozi.mbanefo@unn.edu.ng

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in the predominance of steroid sensitivity, with steroid-resistant nephrotic syndrome (SRNS) assuming prominence as the more common variant worldwide.[7-12] Furthermore, a recent systematic review had confirmed high prevalence rates of histopathological subtypes associated with steroid resistance in sub-Saharan African setting.[13]

In Nigeria, although previous studies found a similar trend,[14,15] recent findings from other regions of the country have reported a rise in the incidence of SSNS.[16-18] In Enugu, the epidemiological pattern of CNS was reported two decades ago by Okoro *et al*.[19] However, there is no recent study in this locality indicating the current pattern or a similar rise in the incidence of SSNS as reported elsewhere in Nigeria. This study therefore aimed to determine the pattern of steroid sensitivity and steroid resistance in childhood idiopathic nephrotic syndrome (INS) as seen at a tertiary hospital in Enugu, south-east Nigeria.

Materials and Methods

The present study was a retrospective, observational descriptive study of children diagnosed with INS. Those with secondary nephrotic syndrome were excluded from the study. It was conducted at the Pediatric Nephrology Clinic of the University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, over 5 years, from 2016 to 2020. The hospital is a tertiary health institution run by the central (Federal) government and was established primarily for the patients domiciled in the south-eastern part of Nigeria and beyond. Ethical approval was obtained from the Health Research and Ethics Committee of the hospital before commencement of the study. All subjects enrolled in this research have responded to an informed consent which has been approved by the local Ethics Committee on Human Research and this protocol has been found acceptable by them. Using a study proforma, we documented the following data from the case files of the children with INS: the demographic variables, clinical data (including steroid-responsive and renal-transplant cases), and histopathological patterns (including indications for renal biopsy). Renal biopsies were studied only by light microscopy due to unavailability of facilities for electron microscopy and immunofluorescence. Data were anonymized to maintain confidentiality and were analyzed on descriptive statistics with frequencies expressed in numbers and percentages. Means of numerical variables were estimated and means of groups were compared with the student's *t*-test. Relationship between two groups was evaluated with the Chi-square test. For these comparisons, the adopted *P* value for statistical significance was <.05.

Definition of terms

Nephrotic syndrome: Diagnosis was made when degree of proteinuria in dipstick urinalysis was 3+ or 4+, or exceeding 40 mg/m^2/hour or spot-urine protein-creatinine ratio of more than 2 mg/mg, and hypoalbuminemia with a serum albumin less than 25 g/L (for the therapeutics, all the children received oral prednisolone at 2 mg/kg/day not exceeding 60 mg for the first two months of therapy before tapering over three months).

Remission: Nil or trace proteinuria (<30 mg/dL or <4 mg/m^2/h) by dipstick for three consecutive days.

SSNS: Achieving remission within four to six weeks of daily oral prednisolone. Early responders achieved remission within the first two weeks, while late responders achieved remission within four to six weeks.

SRNS: Failure to achieve remission after eight weeks of appropriate oral daily dose prednisolone.

Relapse: Recurrence of 100 mg/dL (≥2+) proteinuria by dipstick for three consecutive days after achieving remission.

Steroid-dependent nephrotic syndrome: Two consecutive relapses during alternate day steroid therapy or within two weeks after cessation of steroid.

Frequent relapsing nephrotic syndrome: Two or more relapses within six months of initial response or four or more relapses in any 12-month period.

Results

Demographics and clinical features

Of a total of 150 patients seen over the period, 105 (70%) were males, while 45 (30%) were females, with male/female ratio of approximately 2:1. Ninety six (64%) of the patients were aged between 1 and 10 years, whereas 54 (36%) were preadolescents and adolescents, aged 11-18 years. Forty eight (32%) were aged 1-5 years. The mean age was 8.67 ± 4.69 years. At presentation, all (100%) the affected children had recurrent generalized body swelling. Hematuria and oliguria were seen in 52 children (34.6%), while hypertension and leukocyturia were seen in 23 (15.3%) and 45 (30%) children, respectively [Table 1]. The mean values of some biochemical variables at presentation were calculated as follows: serum albumin was 18.25 ± 4. 04 g/L, urine protein/creatinine ratio (spot-urine protein) was 6.34 ± 4.60 mg/mg, serum cholesterol was 8.76 ± 1.83 mmol/L, while estimated glomerular filtration rate was 112.93 ± 59.39 mL/min/1.73 m^2.

Responses to steroid therapy

One hundred and six (70.7%) of the patients initially had SSNS, of whom 12 (11.3%) and eight (7.5%)

later became frequent-relapsers and steroid-dependent patients, respectively. Notably 44 (29.3%) patients were steroid-resistant. The mean age of patients with SSNS was 7.08 ± 4.3 years, while that of patients with SRNS was 12.52 ± 3.05 years. The highest percentage (95.8%) of steroid sensitivity was found in patients aged 1 to 5 years. Only four (2.7%) had remained in full remission for at least 3 years.

Steroid sensitivity versus patient's age

The relationship between steroid sensitivity and patient's age was evaluated. As shown in Table 2, steroid sensitivity among the patients was significantly related to younger age group, whereas steroid resistance was significantly related to older age group (χ^2 = 45.414, P < .001). This finding suggests that steroid sensitivity may be age-dependent.

Similarly, in comparing the mean ages of patients with SSNS with those with SRNS, their mean ages were 7.08 ± 4.31 years and 12.52 ± 3.05 years, respectively (t = 7.619, P < .001), indicating that the mean age of children with SRNS was significantly higher than those with SSNS.

Table 1: Demographics and clinical features of the patients with childhood nephrotic syndrome

Parameters	Frequency (*n*)	Percentage
Gender*		
Male	105	70.0
Female	45	30.0
Age (years)**		
1-5	48	32.0
6-10	48	32.0
11-15	41	27.3
16-20	13	8.7
Clinical features of NS		
Generalized body swelling	150	100.0
Hematuria	52	34.6
Oliguria	52	34.6
Hypertension	23	15.3
Leukocyturia	45	30.0

NS, Nephrotic syndrome. *Male/Female ratio=2:1 **Mean age=8.67±4.69 years

Table 2: The relationship between steroid sensitivity and patient's age group

Age group (years)	Steroid-sensitive nephrotic syndrome (*n*=106) (%)	Steroid-resistant nephrotic syndrome (n=44) (%)	χ^2	*P**
1-5	46 (43.4)	2 (4.5)	45.414	<0.001
6-10	39 (36.8)	9 (20.5)		
11-15	14 (13.2)	27 (61.4)		
16-20	7 (6.6)	6 (13.6)		

*P<0.05 taken as statistically significant

Outcomes of SRNS cases

Sixty eight patients had renal biopsy and 42 (61.76%) of them were due to SRNS. Eleven (7.3%) of those with SRNS received calcineurin inhibitors and 12 (8%) progressed to end-stage renal disease, of which four (2.7%) had a successful renal transplant with a living unrelated donor in a private facility within the country. Five (3.3%) died due to inability to afford renal replacement therapy. The rest were lost to follow-up.

Indications for renal biopsy and histopathological patterns

The most common indication for renal biopsy was SRNS. Seven (10.29%), eight (11.76%), and 11 (16.17%) were due to frequent relapses, steroid dependence, and age at an onset of more than 10 years, respectively. One of those with steroid dependence relapsed after 2 years in remission. Three children declined due to sociocultural reasons and financial constraints, as the caregivers paid for the procedure out-of-pocket. Three had a repeat due to previous inconclusive results.

The most common histopathological pattern was focal segmental glomerulosclerosis (FSGS) (43/68, 63.2%). Other patterns, in the order of frequency, were mesangio-proliferative glomerulonephritis (15/68, 22.0%), membrano-proliferative glomerulonephritis (MPGN) (7/68, 10.0%), minimal change nephrotic syndrome (2/68, 3.1%), and membranous glomerulonephritis (1/68, 1.5%) [Figure 1].

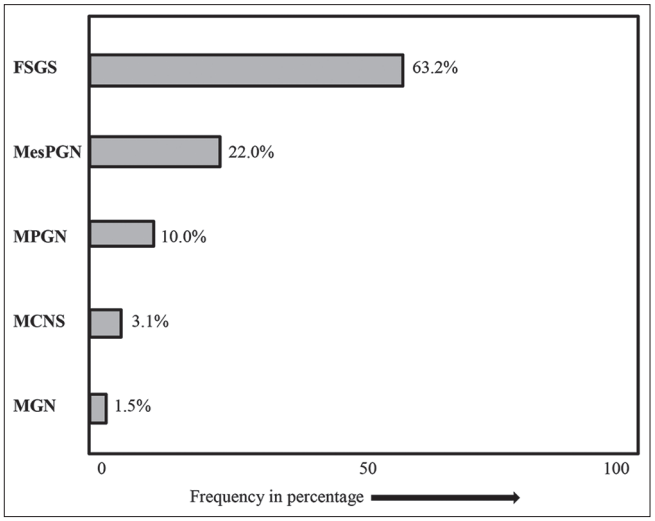

Figure 1: The histopathological patterns in patients with steroid-resistant nephrotic syndrome. FSGS, Focal segmental glomerulosclerosis; MesPGN, Mesangioproliferative glomerulonephritis; MPGN, Membranoproliferative glomerulonephritis; MCNS, Minimal change nephrotic syndrome; MGN, Membranous glomerulonephritis

Table 3: Comparative analysis of studies conducted in different regions of Nigeria on childhood nephrotic syndrome

Parameters	Okoro *et al*.,[19] Enugu, southeast Nigeria (2000)	Mbanefo *et al*.† Enugu, Southeast Nigeria (2022)	Asinobi *et al*.,[16] Ibadan, Southwest Nigeria (2019)	Olowu *et al*.,[21] Ile-Ife, Southwest Nigeria (2010)	Esezobor *et al*.,[18] Lagos, Southwest Nigeria (2020)	Anochie *et al*.,[20] Port-Harcourt, Southern Nigeria (2006)	Anigilaje *et al*.,[17] Abuja Northcentral Nigeria (2019)
Gender	M > F	M > F	M > F	M > F	M > F	M=F	M > F
Age (years)	2-16	1-18	1-15	2.5-14	1-17	1-16	1.5-18
Mean age (years)	7.9±3.4	8.67±4.69	7.9±3.7	8.3±3.5	6.6±4.2	5.8±3.8	8.2±4.4
Idiopathic NS	N/A	78.7%	N/A	69.2%	94.0%	71.4%	89.1%
Secondary NS	N/A	21.3%	N/A	30.8%	5.85%	14.3%	10.0%
SSNS	30.0%	70.6%	63.3%	45.2%	85.9%	80.0%	73.9%
SRNS	70.0%	29.3%	36.7%	54.8%	5.85%	20.0%	26.1%
Number of renal biopsies	4	68	78	54	23	4	5
Histopathological types							
FSGS	25%	63.2%	60.0%	39.1%	19	50.0%	60.0%
MesPGN	N/A	22.0%	N/A	8.7%	1	N/A	N/A
MPGN	50.0%	10.3%	27.0%	43.5%	N/A	N/A	N/A
MGN	N/A	1.47%	N/A	N/A	1	N/A	N/A
MCNS	25%	2.94%	3.0%	4.35%	1	25.0%	20.0%
Inconclusive reports	N/A	N/A	N/A	N/A	N/A	25.0%	20.0%

M, Male; F, Female; NS, Nephrotic syndrome; SSNS, Steroid-sensitive nephrotic syndrome; SRNS, Steroid-resistant nephrotic syndrome; FSGS, Focal segmental glomerulosclerosis; MesPGN, Mesangial proliferative glomerulonephritis; MPGN, Membranoproliferative glomerulonephritis; MCNS, Minimal change nephrotic syndrome; N/A, Not available. †Present study

Study drop-outs

Twenty one children were excluded from the study. While seven children were excluded due to missing or incomplete data, 14 were lost to follow-up. Thus, steroid response could not be documented.

Discussion

Despite the reported global predominance of SSNS in childhood, emerging evidence from several studies previously suggest a change in the trend toward SRNS. These reports emanate particularly from countries with predominant Black population. The present study was thus conducted in a sub-Saharan African setting with overwhelming majority of Black children to ascertain if there is a rising incidence of SSNS in recent years.

The present study has demonstrated that the number of children with SSNS is still relatively high, although a substantial proportion of them are diagnosed with SRNS. This finding contradicts that of the previous study in this center by Okoro *et al*.,[19] who reported a higher percentage of SRNS in children. This disparity can be attributed to the predominant histopathologic types (FSGS and MPGN) which the authors reported among their patients. Also, the increasing sensitivity to steroid therapy (from 30% initially reported in the previous study by Okoro *et al*.,[19] to as high as 71% in this present study after two decades) is consistent with the findings of studies from other regions in the country[16-18] [Table 3]. These studies[16-18] were notably recent, published less than 3 years ago. However, two studies published more than a decade ago indicate a predominant picture of steroid sensitivity[20] and that of steroid resistance.[21] The longer duration of 8 weeks on daily oral prednisolone (previously 4 weeks)—which allowed late responders to achieve remission—may account for this high prevalence in steroid-sensitivity patterns seen in different regions of the country.[16-18,20] Again, our 70.6% in SSNS is only comparable to 63.3% and 73.9% reported in Ibadan (southwest Nigeria)[16] and Abuja (northcentral Nigeria),[17] respectively. It is less than the 80.0% documented in Lagos (southwest Nigeria) by Esezobor *et al*.[18] and Ladapo *et al*.[22] We speculate that the differences may due to recruitment of much younger population and possible genetic predisposition given that Lagos is a multiethnic cosmopolitan city. On the other hand, our finding of a higher percentage of SRNS when compared with recent studies in Lagos[18] and Abuja[17] is attributed to possible genetic and ethnic factors, as our study population predominantly consisted of the Igbo ethnic group. A similar steroid-responsive pattern was reported in the same ethnic group within the south-west Nigerian city of Lagos despite the geographic dissimilarity.[18] Again, the lower percentage of SSNS found in this study when compared to 80% to 90% reported globally[3] affirmed the predominance of SRNS

in Black population. Nevertheless, there appears to be a changing trend in the prevalent histopathologic types globally which may account for the rising incidence in steroid-resistance over the years. For instance, our study and those from other regions of the country[16-18,20,21] show that FSGS and MPGN (associated with steroid-resistance) were the predominant histopathologic types. Contrary to the study by Olowu *et al*.[21] in Ile-Ife (southwest Nigeria) where MPGN predominated, the preponderance of FSGS among those with SRNS in our study is similar to reports from several other parts of the country including the northwestern city of Kano,[23] southern city of Port-Harcourt,[20] southwestern city of Lagos,[18,21] northcentral city of Abuja,[17] and southwestern city of Ibadan.[15] These findings demonstrate that genetic, ethnic, and geographic factors may influence the epidemiology of childhood NS. Some authors believe that there has been a transition from quartan malarial nephropathy through MPGN to FSGS within Nigeria in recent times.[24] It is worthy to mention that the abnormally low minimal change disease found in this study is attributed to the dominance of recruitment of cases with steroid resistant for kidney biopsy which they are globally reported not to be.[1,3] To explain the high prevalence of steroid-sensitivity in our study and elsewhere in the country, we align with the suggestion that minimal change nephrotic syndrome and FSGS may occupy the extreme ends of the same disease-spectrum given the similarity in their electron microscopic findings but dissimilarity in their light microscopic findings.[25] Additionally, the increasingly reported cases of FSGS may be explained by recently identified APOL 1-associated FSGS (linked to the APOL-1 gene common in the Black race)[26] and the viral-mediated FSGS due to the human immunodeficiency virus pandemic.[27]

In this study, there was a significant decline in steroid sensitivity and a corresponding rise in steroid resistance with increasing age. However, a slight change in the steroid sensitivity pattern was noted in much older children aged 16-20 years (diagnosed at age less than 18 years but yet to transition to adult clinic), a finding we attribute to possible hormonal influence and transition to adulthood. Expectedly, there was a male preponderance in our study as previously documented in other studies except for the study by Anochie *et al*.,[20] who reported equal numbers of both gender in their study. Again, the mean age of our patients is slightly more than the previous finding noted by Okoro *et al*.,[19] in our clime most likely because of the recruitment of older children in the present study.

We therefore suggest a prospective longitudinal study to obtain a more reliable documentation of incident cases of either SSNS or SRNS. Besides, a multicenter study in the south-eastern region of the country (which will involve a larger population of subjects) may help to provide the correct picture of the changing trend in steroid-responsiveness among children with INS in this clime.

Our study has some limitations. First, histopathological diagnosis of renal biopsy specimens was only made by light microscopy as paucity of appropriate facilities precluded diagnosis by electron microscopy and immunofluorescence. Second, the retrospective nature of the study has its drawbacks, especially the challenge of incomplete data.

Conclusions

This study has shown that there has been an increase in the cases of SSNS in the south-east Nigerian city of Enugu over a decade now. Notwithstanding this trend, there is equally an increased incidence of SRNS when compared to other regions in the country. The prevalent histopathologic type, namely FSGS, may explain this finding. More importantly, the therapeutic implication is that there would most likely be a paradigm shift from the less expensive corticosteroids to the more expensive and less affordable calcineurin inhibitors in a low-income setting like Nigeria.

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Conflicts of interest

There are no conflicts of interest.

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